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Clinical paper

Usefulness of neuron specific enolase in prognostication after cardiac arrest: Impact of age and time to ROSC[☆]



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Abstract

Aim of the study: We evaluated the impact of patient age and time from collapse to return of spontaneous circulation (ROSC) on the prognostic accuracy of neuron specific enolase (NSE) after out-of-hospital cardiac arrest (OHCA).

Methods: Using electrochemiluminescence immunoassay, we measured serum concentrations of NSE in 249 patients who were admitted to intensive care units after resuscitation from OHCA. In each quartile according to age and time to ROSC, we evaluated the ability of NSE at 48 h after OHCA to predict poor outcome (Cerebral Performance Category 3–5) at 12 months.

Results: The outcome at 12 months was poor in 121 (49%) patients. The prognostic performance of NSE was excellent (area under the receiver operating characteristic curve, AUROC, 0.91 [95% confidence interval, 0.81–1.00]) in the youngest quartile (18–56 years), but worsened with increasing age, and was poor (AUROC 0.53 [0.37–0.70]) in the oldest quartile (72 years or more). The prognostic performance of NSE was worthless (AUROC 0.45 [0.30–0.61]) in the quartile with the shortest time to ROSC (1–13 min), but improved with increasing time to ROSC, and was good (AUROC 0.84 [0.74–0.95]) in the quartile with the longest time to ROSC (29 min or over).

Conclusion: NSE at 48 h after OHCA is a useful predictor of 12-month-prognosis in young patients and in patients with a long time from collapse to ROSC, but not in old patients or patients with a short time to ROSC.

Keywords: Neuron specific enolase (NSE), OHCA, Resuscitation, Cardiac arrest, Neurological outcome, Biomarkers

[☆] Some of the results were presented as an abstract at the 37th International Symposium on Intensive Care and Emergency Medicine, 21–24 March 2017, Brussels, Belgium.

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Introduction

After cardiac arrest and resuscitation, prognostication is challenging.^{1,2} In addition to clinical neurological examination, imaging and neurophysiological studies, certain biomarkers, particularly neuron specific enolase (NSE), are considered useful.^{3–7} Sedative medications affect clinical examination and electroencephalography (EEG) but not biomarkers.⁷ Hypoxic brain injury increases blood NSE concentrations⁸ and international guidelines recommend the use of NSE as one part of multimodal prognostication.⁶

However, also other factors than hypoxic brain damage may elevate the NSE concentration^{4,8–14} and a good outcome is possible despite high concentrations.^{8,15–17} In addition, NSE concentrations can remain low despite severe brain damage.¹⁵

It is not known whether age affects the prognostic ability of NSE after cardiac arrest. Moreover, the time from collapse to the return of spontaneous circulation (ROSC) probably affects the severity of hypoxic-ischemic brain injury, a typical cause of death after cardiac arrest,¹⁸ but it is unknown if this affects the prognostic value of NSE.

We aimed to evaluate the impact of the patient's age and time from collapse to ROSC on the ability of NSE to predict poor long-term outcome in patients resuscitated from out-of-hospital cardiac arrest (OHCA).

Methods

Study population

This study is a sub-study of the FINNRESUSCI study.¹⁹ In brief, the FINNRESUSCI study prospectively collected data on 504 adult patients who were treated in 21 Finnish intensive care units (ICUs) after OHCA between March 1st, 2010, and February 28th, 2011. In the current study we included 249 unconscious patients, for whom blood samples were available. The FINNRESUSCI study protocol was approved by the Ethics Committee of Helsinki University Hospital and by each participating hospital.

We assessed neurological outcome according to the Cerebral Performance Category (CPC)²⁰ at 12 months after cardiac arrest. We determined good outcome as sufficient neurological function for managing activities of daily living independently (CPC 1–2) and poor outcome as severe neurological deficits or death (CPC 3–5). The cause of cardiac arrest (cardiogenic or other) was determined with clinical criteria. We chose death in hospital as a secondary outcome.

Data collection

Patient data were collected by using Internet-based case report forms. Data on previous state of health was collected from the patient's medical history and mortality data were obtained from Statistics Finland. Neurological status of all patients at 12 months after cardiac arrest was assessed by phone contact between the patient and a specialist in neurology who was blinded to treatment details. A structured interview to determine the Pittsburgh Cerebral Performance Category (CPC) was used.

Blood sampling and biomarker analysis

Blood samples were taken at 24 and 48 h after cardiac arrest. The blood sample was allowed to clot at room temperature for 60 min, after

which it was centrifuged and the obtained serum stored at -70°C . Serum concentrations of NSE were measured with a commercially available electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany) in April 2015. All analyses were made in the same laboratory. The range of measurements was 0.05–370 $\mu\text{g/l}$ (or up to 740 $\mu\text{g/l}$ for 2-fold diluted samples) and the range of normal values was 0–16.3 $\mu\text{g/l}$. The intra and inter assay coefficients of variation were $< 3.9\%$ and $< 3.2\%$, respectively. We considered a concentration of 500 mg/l or higher of free haemoglobin as an indicator of significant haemolysis.³ In line with a real-life situation in Finland, we included all blood samples to the study regardless of the amount of haemolysis.

Statistical analysis

We present continuous data as medians with interquartile ranges (IQRs) and categorical data as absolute numbers with percentages (95% confidence intervals [CIs]). We tested normality of distribution with the Kolmogorov–Smirnov test. We used the independent samples *t* test to compare continuous data with normal distributions. When the distribution was not normal, we used the Mann–Whitney *U* test or the Kruskal–Wallis test, as appropriate. We compared categorical variables by using Pearson's Chi test or Fisher's exact test, as appropriate.

To assess the ability of NSE to discriminate between patients with poor outcome (CPC 3–5) and those with good outcome (CPC 1–2), we calculated areas under the receiver operating characteristic curves (AUROCs)²¹ with 95% CIs. We defined values < 0.7 as poor, values of 0.7–0.8 as satisfactory, 0.8–0.9 as good and values > 0.9 as excellent. In addition to NSE levels at 24 h and 48 h after cardiac arrest, we also studied the change in NSE between 24 h and 48 h after cardiac arrest. We determined IQRs for patient's ages and the times from collapse to ROSC, and for every quartile we calculated the AUROC for NSE at 48 h. We compared AUROCs by using the bootstrap method. Based on the sensitivity and specificity for different cut-off values, we selected cut-offs using the Youden index.^{22,23} We also determined the cut-off value for 99% specificity. We calculated the sensitivity, specificity, positive predictive value (PPV) and positive likelihood ratio (LR+) for these cut-off values.

We used logistic regression analysis to create a baseline multivariate model to predict poor outcome. We evaluated the predictive value of this model by determining the AUROC. We also assessed the continuous Net Reclassification Improvement (NRI) achieved by the addition of NSE into the baseline model. We assessed event NRI (NR_{Ie}) and non-event NRI (NR_{Ine}). NR_{Ie} is calculated as [(the number of individuals with the predicted event, i.e. poor outcome, given a higher risk after addition of NSE) – (the number of individuals with the event given a lower risk)]/[the number of individuals with the event]. Likewise, NR_{Ine} is the net proportion of individuals without the event given a lower risk. The overall NRI is the sum of NR_{Ie} and NR_{Ine}. The theoretical range of values for both NR_{Ie} and NR_{Ine} is -1 to $+1$, and that of the overall NRI is -2 to $+2$.^{24,25}

In addition, we determined the Integrated Discrimination Improvement (IDI) achieved by the addition of NSE into the baseline multivariate model. IDI measures not only the direction of the change in probability with the addition of new information, but also the magnitude of the change. We calculated event IDI (ID_{Ie}) for patients with poor outcome as [(mean probability of poor outcome with baseline model + NSE) – (mean probability of poor outcome with baseline model)] and non-event IDI (ID_{Ine}) for patients with good

outcome as [(mean probability of poor outcome with baseline model)–(mean probability of poor outcome with baseline model + NSE)]. IDI is the sum of IDI_e and IDI_{ne}. The theoretical range of IDI_e and IDI_{ne} is–1 to +1 and that of IDI is–2 to +2. ^{24,26}

We considered *p* values <0.05 as significant. We made the analyses with SPSS version 21 (SPSS, Chicago, IL, USA) and R version 3.1.1.

Results

In total, 249 OHCA patients were included in the study (Fig. 1). Blood samples at 48 h were available for 220 patients. Because the consent was not available for all patients at 24 h, samples from this time point are missing for seven patients. The initial rhythm was shockable in 177 (71%) patients. The aetiology of the arrest was cardiac in 199 (79.9%) patients. Targeted temperature management was used in 193 (77.5%) patients. The baseline characteristics of the study population are presented in Table 1.

Patient outcomes and prognostic ability of NSE

Overall, 121 patients (49%) had a poor outcome at 12 months. The median NSE concentration at 24 h was 12.9 µg/l (IQR, 7.6–23.6) in patients with poor outcome and 8.7 µg/l (5.9–13.4) in those with good outcome (*p* < 0.001). The median NSE concentration at 48 h was 17.9 µg/l (8.1–56.4) in patients with poor outcome and 8.2 µg/l (5.9–12.1) in those with good outcome (*p* < 0.001). The ability to predict poor outcome was better for NSE at 48 h (AUROC 0.72 [0.65–0.80]) than NSE at 24 h (AUROC 0.65 [0.58–0.72]), *p* = 0.005.

The AUROC for the change in NSE concentration between 24 h and 48 h after cardiac arrest was 0.70 (0.63–0.78 [*p* < 0.001]), which was not significantly different from the AUROC of NSE at 48 h (*p* = 0.489).

Among those 29 patients, for whom blood samples at 48 h were not available, poor outcome occurred in 23 patients (79.3%), 13 of whom died before the 48 h time point. For these 29 patients, the concentrations of NSE at 24 h were 15.3 µg/l (4.8–47.9) for patients with poor outcome and 6.3 µg/l (2.9–12.5) for those with good outcome.

For three patients, significant haemolysis was found. For two of those patients, with NSE concentrations 36.0 µg/l and 37.0 µg/l,

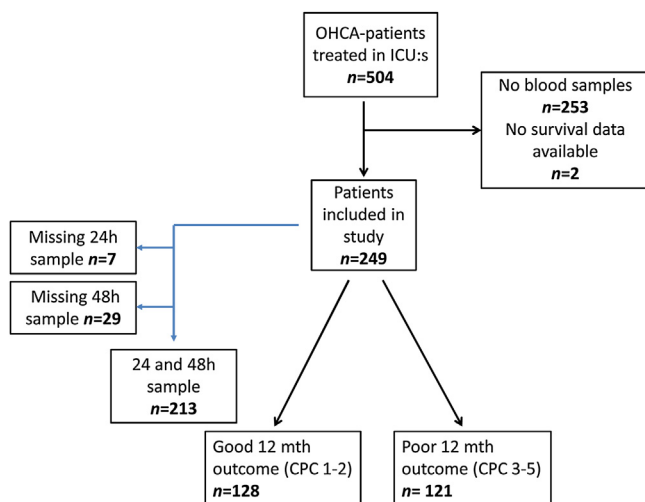


Fig. 1 – Flowchart of the study population.

Table 1 – Baseline characteristics for all patients and stratified according to age and time to ROSC.

All	Age	Time to ROSC					p
		18-56 years	57-63 years	64-71 years	≥72 years	≥29 min	
Number of patients, n	249	62	69	59	59	60	
Age, median (IQR), years	63 (56.5-71.0)	48.0 (42.0-54.0)	60.0 (59.0-62.0)	67.0 (66.0-70.0)	77.0 (73.0-81.0)	62.0 (54.0-69.0)	
Gender, males, n, (%)	209 (83.9)	50 (80.6)	60 (87.0)	52 (88.1)	47 (79.7)	51 (85.0)	
Witnessed, n (%)	227 (91.2)	56 (90.3)	68 (98.6)	51 (86.4)	52 (88.1)	55 (91.7)	
Bystander CPR, n (%)	146 (58.6)	34 (54.8)	43 (62.3)	41 (69.5)	28 (47.5)	35 (58.3)	
Cardiogenic reason of arrest, n (%)	199 (79.9)	41 (66.5)	57 (82.6)	50 (84.7)	51 (86.4)	47 (76.7)	
Time to ROSC, median (IQR), min	20.0 (13.5-28.0)	20.0 (14.0-29.3)	21.0 (13.0-30.0)	23.0 (16.0-28.0)	19.0 (10.0-24.0)	34.0 (30.3-40.0)	
Shockable rhythm, n (%)	177 (71.1)	42 (67.7)	49 (71.0)	45 (76.3)	41 (69.5)	44 (73.3)	
SAPS II, median (IQR), points	58.0 (42.0-69.0)	52.0 (32.0-61.0)	57.0 (40.0-64.0)	60.0 (42.0-72.0)	67.0 (52.0-73.0)	64.5 (52.3-71.8)	
Poor outcome (CPC 3-5), n (%)	121 (48.6)	25 (40.3)	26 (37.7)	34 (57.6)	36 (61.0)	43 (71.7)	
IQR, interquartile range; Witnessed, witness for collapse; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; Shockable rhythm, ventricular fibrillation or ventricular tachycardia; SAPSII, Simplified Acute Physiology Score, CPC, Cerebral Performance Category.							

IQR, interquartile range; Witnessed, witness for collapse; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; Shockable rhythm, ventricular fibrillation or ventricular tachycardia; SAPSII, Simplified Acute Physiology Score, CPC, Cerebral Performance Category.

	All	Age		Time to ROSC					
		18–56 years	57–63 years	64–71 years	≥ 72 years	1–13 min	14–20 min	21–28 min	≥29 min
NSE 48 h	AUROC	0.72							
	CI (95%)	0.65– 0.80	0.91	0.74	0.76	0.53	0.45	0.62	0.75
	p	<0.001	0.81–1.00	0.60–0.88	0.62–0.90	0.37–0.70	0.30–0.61	0.44–0.80	0.74–0.95
	Sensitivity	50.0	<0.001	0.002	0.002	0.687	0.598	0.132	0.004
	Specificity	92.6	69.6	47.6	56.0	31.0	6.7	27.8	56.7
NSE48h >20 µg/l	PPV	100	100	90.2	91.7	85.7	95.1	97.8	89.5
		84.5	100	71.4	87.5	75.0	33.3	83.3	89.5
	LR+ (95% CI)	6.8 (3.5–13.1)	∞	4.9 (1.7–13.7)	6.7 (1.7–26.5)	2.2 (0.7–7.1)	1.4 (0.1–14.0)	12.5 (1.6–99.7)	5.4 (1.4–20.7)
	p	<0.001	<0.001	0.003	0.001	0.201	1.00	0.006	0.002
	Sensitivity	35.7	47.8	33.3	40.0	24.1	6.7	11.1	36.7
NSE 48h >37 µg/l	Specificity	99.2	100	100	100	95.2	97.6	100	100
	PPV	97.2	100	100	100	87.5	50.0	100	100
	LR+ (95% CI)	43.6 (6.1–312.4)	∞	∞	∞	5.1 (0.7–38.2)	2.7 (0.2–41.0)	∞	∞
	p	<0.001	<0.001	<0.001	0.001	0.117	0.468	0.078	0.003
									<0.001
ROSC, return of spontaneous circulation; AUROC, area under the receiver operating characteristic curve; PPV, positive predictive value; LR+, positive likelihood ratio.									

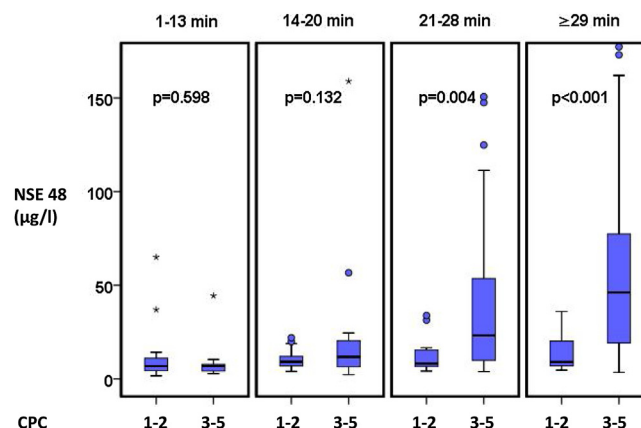


Fig. 3 – Distribution of NSE concentrations ($\mu\text{g/l}$) at 48 h for the patients with good (Cerebral Performance Category, CPC 1–2) and poor (CPC 3–5) outcome in quartiles according to time from collapse to ROSC.

Boxplot figures; each box showing the interquartile range, with a horizontal line inside the box showing the median value; bars showing the range of values except outliers (circles and stars), defined as values more than 1.5 box lengths from the edge of the box.

poor outcome in different groups according to time to ROSC is presented in Table 2. The prognostic value was poor in the first quartile (1–13 min), but improved with increasing time to ROSC, and was good for patients with the longest time to ROSC (≥ 29 min).

The ability of NSE at 48 h to predict death in hospital in different quartiles according to time to ROSC is presented in the Supplementary material, Table S3.

The main results remained essentially unchanged after exclusion of the patients with haemolytic blood samples (Supplementary material, Table S4).

The value of NSE in addition to other prognostic data

Our baseline risk prediction model including age, time to ROSC, initial rhythm and Simplified Acute Physiology Score (SAPS) II points²⁷ without age points had an AUROC of 0.81 (0.75–0.86) for predicting poor outcome at 12 months. When 48 h NSE was added to this model, the AUROC increased to 0.84 (0.79–0.89) ($p=0.021$).

Regarding different age groups, adding NSE to the baseline risk prediction model improved the AUROC only for the youngest patients (18–56 years) ($p=0.013$).

Considering different times to ROSC, adding NSE to the baseline model improved the AUROC only for patients with longest time to ROSC (29 min or more) ($p<0.001$).

AUROC, NRI and IDI data for all patients and according to age and time to ROSC quartiles are presented in Table 3.

NSE analyses were available in 9 of 21 participating hospitals at the time of the FINNRESUSCI study. These hospitals treated 35.3% of the study patients. The prognostic ability of NSE was dependent on age and time to ROSC in both hospital groups (Supplementary Tables S5 and S6).

Discussion

The main finding of our study is that the ability of NSE to predict one-year outcome was dependent on both the patient's age and the time

from collapse to ROSC. In young patients, NSE at 48 h had an excellent predictive value, whereas the predictive value was poor in the oldest patients. For patients with a short time from collapse to ROSC, NSE at 48 h was not able to predict outcome, but it showed a good predictive ability for patients with a long time to ROSC. These findings are important as NSE is one of the parameters commonly used in prognostication of patients resuscitated from cardiac arrest. Further refinement of the use of NSE by identifying appropriate and inappropriate patient groups is of great importance.

We suggest that there may be a plausible explanation for our findings: NSE is a marker of neurological injury, but it may not be able to predict a poor long-term prognosis that is caused by other factors than hypoxic brain injury. For young patients, poor outcome after cardiac arrest is often associated with hypoxic brain damage, whereas poor long-term outcome in elderly patients may often be influenced by other factors (e.g. heart failure, pulmonary or renal disease, infirmity), i.e. factors that may not be reflected by post-resuscitation NSE levels. For patients who die after initially successful resuscitation, hypoxic brain injury is the most common cause of death, but deaths because of circulatory failure also occur frequently.²⁸

In the normal population, NSE levels do not vary significantly in different ages.²⁹ However, in patients with Alzheimer's disease, NSE concentrations in serum tend to decrease with increasing severity of brain atrophy.³⁰ It might be possible that Alzheimer's disease and other neurodegenerative disorders that are more common among the old than in younger people may cause loss of neuronal tissue, which might decrease the response of increasing NSE concentrations after hypoxic brain injury.

In addition to age, the time from collapse to ROSC influenced the ability of NSE to predict poor outcome. NSE at 48 h showed good predictive ability for patients with a long time to ROSC, but not for those with a short time to ROSC. A possible explanation is that for cardiac arrest patients with a long time to ROSC, the cause of poor outcome is often hypoxic brain injury that typically causes high NSE concentrations, whereas a poor outcome despite a short time to ROSC may not be caused by hypoxic encephalopathy, but rather the underlying conditions responsible for the cardiac arrest. In the study by

Table 3 – Multivariate models to predict poor outcome at 12 months (A). Area under receiver operating characteristic curve (AUROC), Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) for all patients and stratified according to age and time to ROSC (B).

		OR (95% CI)							p	
Age ^a		1.045 (1.018–1.074)							0.001	
ROSC ^a		1.076 (1.042–1.112)							<0.001	
Witnessed ^a		0.319 (0.101–1.011)							0.052	
Shockable ^a		0.309 (0.152–0.627)							0.001	
*SAPSII ^a		1.041 (1.019–1.064)							<0.001	
NSE48 ^b		1.055 (1.025–1.085)							<0.001	
		ALL	18–56	57–63	AGE, years 64–71	≥72	1–13	Time to ROSC, min		≥29
								14–20	21–28	
AUROC (95% CI)	Baseline model	0.81 (0.75–0.86)	0.82 (0.71–0.93)	0.84 (0.74–0.95)	0.82 (0.71–0.94)	0.68 (0.52–0.84)	0.72 (0.58–0.86)	0.80 (0.68–0.91)	0.83 (0.71–0.95)	0.71 (0.54–0.87)
	Baseline model + NSE 48 h	0.84 (0.79–0.89)	0.88 (0.79–0.97)	0.88 (0.79–0.97)	0.84 (0.73–0.95)	0.67 (0.52–0.82)	0.68 (0.54–0.83)	0.82 (0.71–0.93)	0.85 (0.75–0.96)	0.90 (0.82–0.99)
p value for difference		0.021	0.013	0.226	0.665	0.819	0.100	0.453	0.561	0.001
NRI	Continuous	0.394	0.773	0.516	0.457	–0.332	–0.491	0.244	0.628	1.140
	NRI _e	–0.082	0.217	–0.143	0.040	–0.379	–0.467	–0.444	–0.067	0.257
		NRI _{ne}	0.476	0.556	0.659	0.417	–0.024	0.688	0.695	0.883
IDI	IDI	0.032	0.141	0.035	0.017	–0.077	–0.059	0.000	0.039	0.228
	IDI _e	–0.010	0.078	–0.017	–0.035	–0.041	–0.039	–0.046	–0.013	0.036
		IDI _{ne}	0.041	0.063	0.052	0.051	–0.035	0.047	0.051	0.192

ROSC, return of spontaneous circulation; Witnessed, witnessed cardiac arrest; Shockable, shockable initial rhythm (ventricular fibrillation or ventricular tachycardia); SAPSII, Simplified Acute Physiology Score II; NSE48, NSE concentration at 48 h after cardiac arrest; AUROC, the area under the receiver operating characteristic curve; NRI, net reclassification improvement; NRI_e, event NRI; NRI_{ne}, non-event NRI; IDI, integrated discrimination improvement; IDI_e, event IDI; IDI_{ne}, non-event IDI.

*SAPSII without age points.

^a Variables in baseline model. Calculated with logistic regression for 220 patients for whom NSE at 48 h was available.

^b NSE at 48 h added to the baseline model.

Streitberger et al. on 1053 resuscitated patients, the cause of death was other than hypoxic brain injury for the majority of patients who died even though the NSE concentration was 17 µg/l or lower.⁴

In our study, the cut-off obtained with the Youden method was 20 µg/l, whereas it was 29 µg/l in the study by Stammet et al. For a 99% threshold of specificity, the cut-off was 37 µg/l, as compared to 68 µg/l in the study by Stammet et al. Requiring 100% specificity results in low sensitivity, which limits the clinical use of biomarkers, and a lower specificity for cut-off values has been proposed by Stammet et al.³¹

Optimal cut-off values for NSE at 48 h to predict poor neurological outcome have varied between 25 and 97 µg/l in different studies.^{4,11,15} There are several possible explanations for the large variation: there are differences in laboratory methods,³² in patient case-mix,^{4,15} in definitions of poor outcome¹⁵ and in the time between the cardiac arrest and the assessment of neurological outcome.^{3–4,16,33–36} Commonly, outcome has been determined at six months after cardiac arrest,^{3,16,36} whereas we assessed outcome at 12 months.

For some individuals, NSE concentrations after cardiac arrest and resuscitation may be high although their prognosis is good.^{8,15–17} Also, ischaemic or haemorrhagic stroke or traumatic intracerebral bleeding increase the serum NSE values, but high levels do not exclude the possibility of a good outcome.^{12–14} In addition, extracerebral sources of NSE may cause bias: high NSE concentrations have been found in association with several diseases, including small cell lung cancer⁹ and many neuroendocrine tumors.³⁷ Therefore, it is advisable to avoid decisions about futility of care on the basis of NSE concentrations alone. Nevertheless, NSE is a useful part of multimodal prognostication based on repeated clinical examination, electrophysiological studies and brain imaging.^{6–7} However, it is important to realise that haemolysis may increase NSE concentrations,^{4,10} and NSE measurements from haemolytic blood samples must not be used for prognostication.

Strengths and limitations

Our study has a number of strengths. This was a nationwide multicentre study with 249 patients. All blood samples were analysed in the same laboratory at one time and long-term neurological outcome was defined by an experienced neurologist blinded to the NSE results.

There are also limitations. Firstly, we did not have blood samples from all FINNRESUSCI study patients. In fact, there was a difference in the proportion of shockable rhythms between our study (71.1%) and the original FINNRESUSCI study (56.8%) and in the proportion of cardiac aetiology of CA (79.9% vs. 66.3). Accordingly, the proportion of patients with good outcome was higher in our study (51%) than in the original FINNRESUSCI study (38.5%), indicating some degree of selection bias. Secondly, we do not know the best CPC or the cause of death of our study patients. Third, the number of patients in the subgroups was rather small.

Conclusions

In this observational study, we found that the ability of NSE at 48 h to predict long-term outcome after resuscitation from OHCA was good for young patients and for patients with a long time from collapse to ROSC, but poor for the oldest patients and for those with a short time to

ROSC. If these findings are confirmed in other studies, they should be taken into account when prognostication guidelines are updated.

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Conflicts of interests

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.resuscitation.2019.04.021>.

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